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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :		(11) International Publication Number:	WO 94/04148
A61K 31/40, 31/445	A1	(43) International Publication Date:	3 March 1994 (03.03.94)

(21) International Application Number: PCT/GB93/01769

(22) International Filing Date: 20 August 1993 (20.08.93)

(30) Priority data:
9218027.2 25 August 1992 (25.08.92) GB

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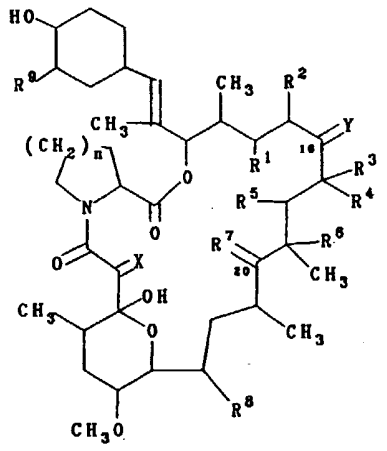
(81) Designated States: AU, CA, JP, KR, NO, NZ, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: USE OF MACROLIDE COMPOUNDS FOR THE TREATMENT OF REVERSIBLE OBSTRUCTIVE AIRWAYS DISEASE



(I)

(57) Abstract

There is provided the use of a compound of formula (I), wherein R^1 and R^2 independently represent H or OH, or they may together represent a second carbon-carbon bond between the carbon atoms to which they are attached; R^3 represents methyl optionally substituted by $-CO_2H$; ethyl optionally substituted by O, OH or $-CO_2H$; propyl optionally substituted by OH or O; or allyl optionally substituted by OH; R^4 represents H; R^5 and R^6 together represent a second carbon-carbon bond between the carbon atoms to which they are attached; R^7 represents O or (H, R^{7a}), where R^{7a} represents H or OH; R^8 and R^9 independently represent OH or OCH_3; X and Y independently represent O or (H, OH); and n represents 1 or 2; in addition to their significances above, R^1 and R^5; R^{7a} and R^8; and R^3, R^4 and Y may form various rings together with the carbon atoms to which they are attached; with certain provisos; and pharmaceutically acceptable derivatives thereof; in the manufacture of a medicament for the treatment of reversible obstructive airways diseases.

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USE OF MACROLIDE COMPOUNDS FOR THE TREATMENT OF REVERSIBLE OBSTRUCTIVE AIRWAYS DISEASE.

This invention relates to a novel treatment of reversible obstructive airways diseases utilizing macrocyclic compounds, and to pharmaceutical formulations including such compounds.

European Patent Application 184162 (to Fujisawa Pharmaceutical Co Ltd) discloses several macrolides (numbered FR-900506, FR-900520, FR-900523 and FR-900525) and derivatives thereof which are isolated from microorganisms belonging to the genus *Streptomyces*. The macrolides are indicated as immunosuppressive agents. European Patent Application 323042 (to Fisons plc) discloses many macrolides which may be derived from those disclosed in European Patent Application 184162. Again, the compounds are primarily indicated as immunosuppressive agents. European Patent Applications 349049, 349061 and 388153 (to Merck & Co Inc) disclose the dihydroxycyclohexyl derivatives of FR-900506, FR-900520 and FR-900523 respectively and indicate them primarily as immunosuppressive agents. European Patent Application 405994 (to Merck & Co Inc) discloses a method of converting compounds such as FR-900506 which contain a piperidine ring into their pyrrolidine ring-containing analogues. European Patent Applications 403242 and 463690 (to Merck & Co Inc) disclose compounds described as antagonists of immunosuppressant macrolides of the FR-900506 type.

None of the documents mentioned above discloses or suggests the use of the compounds disclosed in the treatment of reversible obstructive airways diseases.

International Patent Application WO 90/14826 (to Fisons plc and Fujisawa Pharmaceutical Co Ltd) discloses the use of FR-900506 and macrocyclic compounds related to it in the treatment of reversible obstructive airways diseases. In the compounds specifically mentioned, the C20 position is unsubstituted, the C17 substituent is alkyl or alkenyl and the C16 substituent is O. Such compounds have pronounced immunosuppressive activity.

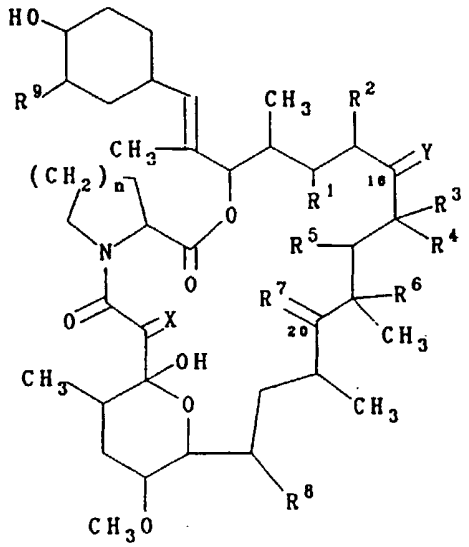
International Patent Application No WO 91/04025 (to Fisons plc) discloses *inter alia* the use of macrocyclic compounds related to FR-900506 in which the C20 position is

substituted by OH and/or the C17 alkyl or alkenyl substituent is substituted by O, OH or CO_2H and/or the C16 position is substituted with (H,OH) in the treatment of immunodepression or a condition involving immunodepression.

European Patent Application 530888 and its equivalent US Patent N° 5.189,042 (to Merck & Co Inc, both published after the priority date of this application) disclose macrocyclic compounds related to FR-900506 in which the C20 position is oxidized or fluorinated. The compounds are indicated *inter alia* in the treatment of reversible obstructive airways diseases.

We have now surprisingly found that macrocyclic compounds of the types disclosed in WO 91/04025, EP 403242 and 463690 are efficacious in the treatment of reversible obstructive airways diseases.

Thus, according to the present invention, we provide the use of a compound of formula I,



I

wherein

R^1 and R^2 independently represent H or OH, or they may together represent a second carbon-carbon bond between the carbon atoms to which they are attached:

R^3 represents methyl optionally substituted by $-CO_2H$; ethyl optionally substituted by O, OH or $-CO_2H$; propyl optionally substituted by OH or O; or allyl optionally substituted by OH;

R^4 represents H;

R^5 and R^6 together represent a second carbon-carbon bond between the carbon atoms to which they are attached;

R^7 represents O or (H,R^{7a}), where R^{7a} represents H or OH;

R^8 and R^9 independently represent OH or OCH_3;

X and Y independently represent O or (H,OH); and

n represents 1 or 2;

in addition to their significances above:

R^1 and R^5 may together represent an oxygen atom, in which case R^6 and R^{7a} together represent a second carbon-carbon bond between the carbon atoms to which they are attached;

R^{7a} and R^8 may together represent an oxygen atom; and

R^3, R^4 and Y, together with the carbon atoms to which they are attached, may represent a methyl-substituted furanyl ring;

but excluding compounds in which together R^2 represents H; R^3 represents methyl, ethyl, propyl or allyl; R^5 and R^6 together represent a second carbon-carbon bond between the carbon atoms to which they are attached; R^8 represents OCH_3; Y represents O; and R^7 represents (H,H);

and pharmaceutically acceptable derivatives thereof;

in the manufacture of a medicament for the treatment of reversible obstructive airways diseases.

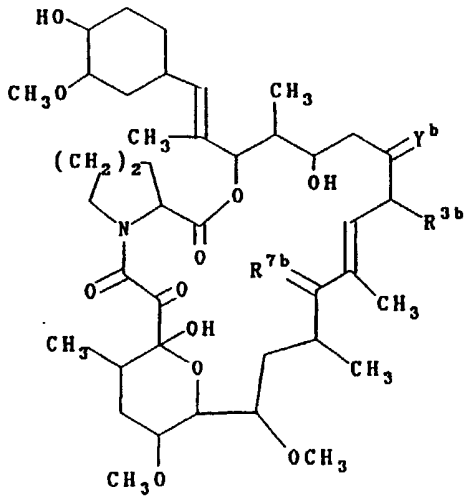
The compounds of formula I and their pharmaceutically acceptable derivatives will be referred to together as 'the compounds of the invention' herein.

Pharmaceutically acceptable derivatives of compounds of formula I include esters (in which the alcohol moiety preferably contains from 1 to 6 carbon atoms), amides (in which the amine moiety preferably contains from 0 to 6 carbon atoms) and salts (preferably alkali metal salts) of any carboxylic acid groups which may be present: and

esters (in which the acid moiety preferably contains from 1 to 6 carbon atoms) of any OH groups which may be present.

The compounds of the invention may be prepared by the methods given in the documents mentioned above, particularly WO 91/04025, EP 403242, EP 463690 and EP 405994 as appropriate. The compounds may also be prepared by total synthesis by modification of the method described by Askin *et al*, J Am Chem Soc, 1989, vol 111(11), p1157.

A preferred group of compounds of formula I are the compounds of formula Ib,



Ib

wherein

R^{3b} represents allyl, or propyl substituted by O;

R^{7b} represents (H,H) or (H,OH); and

Y^b represents O or (H,OH);

but excluding the compound in which together R^{3b} represents allyl, R^{7b} represents (H,H) and Y^b represents O;

and pharmaceutically acceptable derivatives thereof.

Three compounds of formula I (and formula Ib) of particular interest are:

17-allyl-1,14,20-trihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (first disclosed in WO 89/05304, Example 13);

17-(2-Oxopropyl)-1,14-dihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (first disclosed in WO 89/05304, Example 29); and

17-allyl-1,14,16-trihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10-trione (first disclosed in WO 91/04025, Example 13).

The term "treatment" as used herein includes prophylaxis as well as relieving the symptoms of disease.

The term "reversible obstructive airways diseases" will be well understood by those skilled in the art to include conditions such as asthma, including bronchial asthma, allergic asthma, intrinsic asthma, extrinsic asthma and dust asthma, particularly chronic or inveterate asthma (for example late asthma and airway hyper-responsiveness); bronchitis and the like [see for example UK Patent No 2022078 and Brit J Pharmac (1987), 24, 4983-501]. Of particular interest is asthma, and especially its prophylaxis.

The compounds of the invention may be screened for their potential anti-asthma efficacy in the mast cell model described by E Wells, S T Harper, C G Jackson, J Mann and R P Eady in 'Characterization of primate bronchoalveolar mast cells: I. IgE-dependent release of histamine leukotrienes and prostaglandins', J Immunol 137(12): 3933-40, 1986; and 'Characterization of primate bronchoalveolar mast cells: II. Inhibition of histamine LTC4 and PGD2 release from primate bronchoalveolar mast cells and a comparison with rat peritoneal mast cells', J Immunol 137(12): 3941-3945, 1986.

Administration of a compound of the invention may be topical (for example by inhalation to the lung), or systemic (for example by oral administration to the gastrointestinal tract).

Dealing first with topical administration, the compounds of the invention which are solids at room temperature may be inhaled as a dry powder which may be pressurized or non-pressurized. In non-pressurized powder compositions, a compound of the invention in finely divided form may be used in admixture with a larger-sized pharmaceutically acceptable inert carrier comprising particles, eg of up to 100μm diameter. Suitable inert carriers include sugars, for example crystalline lactose. Desirably, at least 95% by weight of the particles of the active ingredient have an effective particle size in the range 0.01 to 10μm.

By providing a large proportion of fine particles of the compound of the invention, a lower dosage may be administered and/or for an equivalent amount of drug to a greater or longer lasting effect is produced, because fine particles are more likely to penetrate into the deeper regions of the human airways.

The compounds of the invention may be finely divided by grinding or milling and are preferably dried thoroughly before formulation.

Non-pressurized powder compositions preferably contain from 0.2 to 5% by weight, more preferably from 0.5 to 2.5% by weight, and particularly from 1 to 1.5% by weight of a compound of the invention, and from 95 to 99.8% by weight, more especially from 98.5 to 99% by weight of the carrier.

Alternatively, the formulation may alternatively be pressurized and contain a compressed gas, eg nitrogen, or a liquefied gas propellant.

In pressurized compositions, the compound of the invention is preferably finely divided, eg having a mass median diameter in the range 0.01 to 10μm (and these finely divided forms of compounds of the invention are a feature of the invention). We particularly prefer the compound of the invention to have a mass median diameter of less than 4μm and especially of less than 3.0μm and most preferably of less than 2.8μm. We also prefer not more than 5% by weight of the particles to have a diameter of greater than 10μm, and more preferably not less than 90% by weight of the particles to have a diameter of less than 6μm.

We prefer pressurized compositions to contain from 0.01 to 5%, more preferably from 0.1 to 1%. and most preferably from 0.1 to 0.5% of a finely divided compound of the invention.

By "mass median diameter" we mean that half the particulate mass is in particles of lesser diameter and half in particles of greater diameter than the specified mass median diameter. The mass median diameter is essentially a Stokes diameter and may be determined using a Joyce Loebl sedimentation disc centrifuge either in a two layer or line start photometric mode [Bagness J and Ottaway A; Proc Soc Analyt Chem, Part 4, Vol 9; (1972) pp83-86].

The liquefied propellant medium, and indeed the total composition, is preferably such that the compound of the invention does not dissolve therein to any substantial extent.

The liquefied propellant is preferably a gas at room temperature (20°C) and atmospheric pressure, i.e. it should have a boiling point below 20°C at atmospheric pressure. The liquefied propellant should also be non-toxic. Among the suitable liquefied propellants which may be employed are dimethyl ether and alkanes containing up to five carbon atoms, eg butane or pentane, or a lower alkyl chloride, eg methyl, ethyl or propyl chlorides. The most suitable liquefied propellants are the fluorinated and fluorochlorinated lower alkanes such as are sold under the Registered Trade Mark 'Freon' (the use of the latter type of propellants is a matter of current concern, and they may be replaced by a suitable substitute when such is available). Mixtures of the above mentioned propellants may suitably be employed. Examples of these propellants are:

dichlorodifluoromethane ('Propellant 12'),
1.2-dichlorotetrafluoroethane ('Propellant 114')
trichloromonofluoromethane ('Propellant 11'),
dichloromonofluoromethane ('Propellant 21'),
monochlorodifluoromethane ('Propellant 22'),
trichlorotrifluoroethane ('Propellant 113'), and
monochlorotrifluoromethane ('Propellant 13').

Propellants with improved vapour pressure characteristics may be obtained by using certain mixtures of these compounds, eg propellant 11 with propellant 12, or propellant 12 with propellant 114. For example, propellant 12, which has a vapour pressure of about 570kPa (absolute) at 20°C and propellant 114, with a vapour pressure of about 180kPa (absolute) at 20°C, may be mixed in various proportions to form a propellant having a desired intermediate vapour pressure. We prefer compositions which do not contain trichloromonofluoromethane.

It is desirable that the vapour pressure of the propellant employed be between 380 and 500, and preferably between 410 and 470kPa (absolute) at 20°C. Such a propellant mixture is usable safely with metal containers. Other mixtures of propellant 12 with propellant 114, or of propellant 12 with propellant 11, or of propellant 12 with propellant 11 and propellant 114 with absolute vapour pressures at 20°C in the range 230 to 380 kPa are usable safely with specially reinforced glass containers.

The pressurized composition may also contain a surface active agent. The surface active agent may be a liquid or solid non-ionic surface active agent or may be a solid anionic surface active agent. It is preferred to use the solid anionic surface active agent in the form of the sodium salt.

The preferred solid anionic surface active agent is sodium dioctyl-sulphosuccinate.

The amount of the surface active agent required is related to the solids content of the suspension and to the particle size of the solids. In general it is only necessary to use 5-15%, and preferably 5-8%, of the solid anionic surface active agent by weight of the solids content of the suspension.

When a liquid, non-ionic surface-active agent is employed it should have a hydrophile-lipophile balance (HLB) ratio of less than 10. The HLB ratio is an empirical number which provides a guide to the surface-active properties of a surface-active agent. The lower the HLB ratio, the more lipophilic is the agent, and conversely, the higher the HLB ratio, the more hydrophillic is the agent. The HLB ratio is well known and understood by the colloid chemist and its method of determination is described by W

C Griffin in the Journal of the Society of Cosmetic Chemists, Vol 1, No 5, pages 311-326 (1949). Preferably the surface-active agent employed should have an HLB ratio of 1 to 5. It is possible to employ mixtures of surface-active agents, the mixture having an HLB ratio within the prescribed range.

Those surface-active agents which are soluble or dispersible in the propellant are effective. The more propellant-soluble surface-active agents are the most effective.

We prefer the liquid non-ionic surface-active agent to comprise from 0.1 to 2%, and more preferably from 0.2 to 1%, by weight of the total composition. Such compositions tend to be more physically stable on storage.

Among the liquid non-ionic surface-active agents which may be employed are the esters or partial esters of fatty acids containing from 6 to 22 carbon atoms, such as caproic, octoic, lauric, palmitic, stearic, linoleic, linolenic, oleostearic and oleic acids with an aliphatic polyhydric alcohol or its cyclic anhydride such as, for example, ethylene glycol, glycerol, erythritol, arabitol, mannitol, sorbitol, the hexitol anhydrides derived from sorbitol (the sorbitan esters sold under the Registered Trade Mark 'Span') and the polyoxyethylene and polyoxypropylene derivatives of these esters. Mixed esters, such as mixed or natural glycerides, may be employed. The preferred liquid non-ionic surface-active agents are the oleates of sorbitan, eg those sold under the Registered Trade Marks 'Arlacel C' (Sorbitan sesquioleate), 'Span 80' (Sorbitan monooleate) and 'Span 85' (Sorbitan trioleate). Specific examples of other liquid non-ionic surface-active agents which may be employed are sorbitan monolaurate, polyoxyethylene sorbitol tetraoleate, polyoxyethylene sorbitol pentaoleate, and polyoxypropylene mannitol dioleate.

We particularly prefer compositions containing a sorbitan or sorbitol ester, eg sorbitan trioleate, in a mixture of propellants 12 and 114. We prefer the ratio of propellant 12 to 114 to be in the range from 2:1 to 1:1, and preferably about 1.5:1 by weight, i.e. we prefer an excess of propellant 12 over propellant 114.

We prefer packages containing from about 8 to 30ml of formulation, eg a conventional aerosol pressure pack of 10ml. The pack preferably has a valve adapted to deliver unit dosages of between 0.025 and 0.25ml, and preferably 0.05 or 0.1ml, of formulation. We prefer the valve to deliver from 2 to 0.02mg, for example 0.2mg of active ingredient and unit doses of these quantities of the drug are provided.

A suitable dose of active ingredient for administration by inhalation is in the range from 0.001 to 0.1mgkg^{-1}day^{-1}, and preferably 0.01mgkg^{-1}day^{-1}.

Thus, according to a second aspect of the invention, there is provided a pharmaceutical formulation including a compound of the invention, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier, which is adapted for administration by inhalation to the lungs. The formulation may be a pressurized aerosol formulation including a pharmaceutically acceptable aerosol propellant, or a non-pressurized formulation including crystalline lactose.

The pressurized formulations of the invention may be made by mixing the various components at a temperature and pressure at which the propellant is in the liquid phase and the compound of the invention is in the solid phase.

In producing the pressurized compositions and packages of the invention, a container equipped with a valve is filled with a propellant containing the finely-divided compound of the invention in suspension. A container may first be charged with a weighed amount of dry compound of the invention which has been ground to a predetermined particle size, or with a slurry of powder in the cooled liquid propellant. A container may also be filled by introducing powder and propellant by the normal cold filling method, or a slurry of the powder in that component of the propellant which boils above room temperature may be placed in the container, the valve sealed in place, and the balance of the propellant may be introduced by pressure filling through the valve nozzle. As a further alternative a bulk of the total composition may be made and portions of this bulk composition may be filled into the container through the valve. Throughout the preparation of the product care is desirably exercised to minimise the absorption of

moisture. On operating the valve, the powder will be dispensed in a stream of propellant, which will vaporise providing an aerosol of dry powder.

Turning now to systemic administration, the compound of the invention may be formulated together with known adjuvants, diluents or carriers using conventional techniques to produce tablets or capsules for oral administration to the gastrointestinal tract. Suitable doses for such oral administration are in the range from 0.003 to 0.3mgkg^{-1}day^{-1}, for example 0.03mgkg^{-1}day^{-1}.

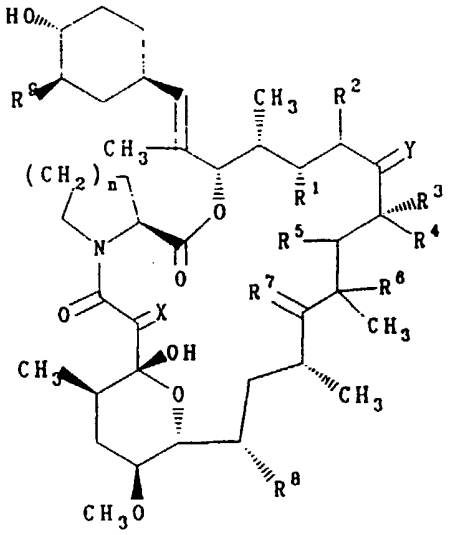
Thus, according to a third aspect of the present invention, there is provided a method of treatment of a reversible obstructive airways disease, which comprises administration of a therapeutically effective amount of a compound of the invention to a patient. The compound may be administered orally to the gastrointestinal tract, or by inhalation to the lungs.

The method of treatment according to the invention has the advantage that the compounds of the invention are more efficacious, less toxic, are longer acting, have a broader range of activity, are more potent, produce fewer side effects, are more easily absorbed or have other useful pharmacological properties, than compounds previously indicated in the treatment of reversible obstructive airways diseases. In particular, the compounds of the invention have a less pronounced immunosuppressive effect than the compounds indicated in WO 90/14826 for the treatment of reversible obstructive airways disease, and hence are more selective.

The dosage to be administered will of course vary with the particular compound of the invention, the condition to be treated and with its severity.

The compound of the invention may be administered as divided doses from 1 to 6, and preferably 2 to 4, times per day. Each dose may comprise 1 or more unit doses.

The invention relates to all stereoisomers of the compounds of the invention. The preferred stereochemistry of certain carbon atoms is indicated in formula Ia.



Ia

wherein R^{1-9}, n, X and Y are as defined above.

The invention is illustrated by the following examples.

Example A

Pressurized aerosol composition

Ingredients:

17-(2-Oxopropyl)-1,14-dihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

(mass median diameter less than 3 microns)	0.054
Sorbitan trioleate	0.091
Propellant 114	7.099
Propellant 12	10.649
	17.893

Method: The sorbitan ester is dispersed in up to half the propellant 12 at -40°C while stirring with a high dispersion mixer. The finely divided compound of the invention is added to the resulting dispersion and disperses in it. The balance of the propellant 12 is then added at -50°C, followed by the propellant 114 also cooled to

-50°C. The resulting mixtures are then filled into vials onto which valves, eg metering valves, are subsequently crimped.

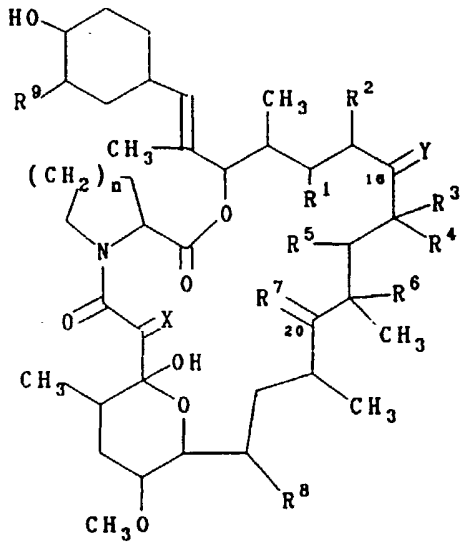
Example B

Mast Cell Screen

17-(2-Oxopropyl)-1,14-dihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone was tested in the screen mentioned above, and found to inhibit histamine release by 50% of its maximum value (IA_{50}) at a concentration of $1x10^{-8}$M.

Claims:

1. The use of a compound of formula I.



I

wherein

R^1 and R^2 independently represent H or OH, or they may together represent a second carbon-carbon bond between the carbon atoms to which they are attached;

R^3 represents methyl optionally substituted by $-CO_2H$; ethyl optionally substituted by O, OH or $-CO_2H$; propyl optionally substituted by OH or O; or allyl optionally substituted by OH;

R^4 represents H;

R^5 and R^6 together represent a second carbon-carbon bond between the carbon atoms to which they are attached;

R^7 represents O or (H,R^{7a}), where R^{7a} represents H or OH;

R^8 and R^9 independently represent OH or OCH_3;

X and Y independently represent O or (H,OH); and

n represents 1 or 2;

in addition to their significances above:

R^1 and R^5 may together represent an oxygen atom, in which case R^6 and R^{7a} together represent a second carbon-carbon bond between the carbon atoms to which they are attached;

R^{7a} and R^8 may together represent an oxygen atom; and

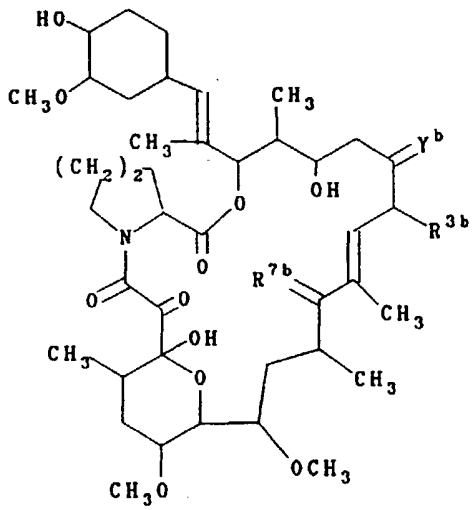
R^3, R^4 and Y, together with the carbon atoms to which they are attached, may represent a methyl-substituted furanyl ring;

but excluding compounds in which together R^2 represents H; R^3 represents methyl, ethyl, propyl or allyl; R^5 and R^6 together represent a second carbon-carbon bond between the carbon atoms to which they are attached; R^8 represents OCH_3; Y represents O; and R^7 represents (H,H);

and pharmaceutically acceptable derivatives thereof;

in the manufacture of a medicament for the treatment of reversible obstructive airways diseases.

2. The use as claimed in claim 1, wherein the compound of formula I is a compound of formula Ib,



Ib

wherein

R^{3b} represents allyl, or propyl substituted by O;

R^{7b} represents (H,H) or (H,OH); and

Y^b represents O or (H,OH);

but excluding the compound in which together R^{3b} represents allyl, R^{7b} represents (H,H) and Y^b represents O;

and pharmaceutically acceptable derivatives thereof.

3. The use as claimed in claim 1 or claim 2, wherein the compound of formula I is 17-allyl-1,14,20-trihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone, or a pharmaceutically acceptable derivative thereof.

4. The use as claimed in claim 1 or claim 2, wherein the compound of formula I is 17-(2-Oxopropyl)-1,14-dihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone, or a pharmaceutically acceptable derivative thereof.

5. The use as claimed in claim 1 or claim 2, wherein the compound of formula I is 17-allyl-1,14,16-trihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10-trione, or a pharmaceutically acceptable derivative thereof.

6. The use as claimed in any one of claims 1 to 5, wherein the reversible obstructive airways disease is asthma.

7. A pharmaceutical formulation including a compound of formula I, as defined in any one of claims 1 to 5, or a pharmaceutically acceptable derivative thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier, which is adapted for administration by inhalation to the lungs.

8. A formulation as claimed in claim 7, which is a pressurized aerosol formulation including a pharmaceutically acceptable aerosol propellant.

9. A formulation as claimed in claim 7, which is a non-pressurized formulation including crystalline lactose.

10. A method of treatment of a reversible obstructive airways disease, which comprises administration of a therapeutically effective amount of a compound of formula I, as defined in any one of claims 1 to 5, or a pharmaceutically acceptable derivative thereof, to a patient.

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/GB 93/01769

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61K31/40 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	EP,A,0 484 936 (FUJISAWA PHARMACEUTICAL CO. LTD.) 13 May 1992 see the whole document especially page 11 line 37-39	1,2,6,10 3,4
X Y	EP,A,0 323 042 (FISONS PLC) July 1989 cited in the application see the whole document especially examples 13 & 29	7-9 3,4
X	WO,A,90 14826 (FUJISAWA PHARMACEUTICAL CO. LTD.) 13 December 1990 cited in the application see the whole document	1,2,5-10

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 October 1993	10.11.93

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	MAIR, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/GB 93/01769

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,91 04025 (FISONS PLC) 4 April 1991 cited in the application see the whole document especially page 5, line 7-10 & 23-26; example 13 -----	1-10

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB93/01769

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
REMARK: Although claim 10 is directed towards a method of treatment of the human/animal body the search has been carried out and directed towards the alleged effects of the compounds.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.
PCT/GB 93/01769

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0484936	13-05-92	AU-A-	8709991	14-05-92
		CA-A-	2054983	09-05-92
		CN-A-	1061907	17-06-92
		JP-A-	5155770	22-06-93
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		CA-A-	2054203	07-12-90
		EP-A-	0475994	25-03-92
		JP-T-	5503283	03-06-93
WO-A-9104025	04-04-91	EP-A-	0491797	01-07-92
		JP-T-	5500215	21-01-93